Q1

methods of the present invention that nuclear transfer generated cells having allogeneic mitochondria are not rejected when transplanted into the nuclear donor. --

The paragraph beginning on line 10 of page 7 (line 17 of page 7 of the substitute specification) is amended as follows:

-- For instance, according to a report in the New York Times on November 12, 1998 (Nicholas Wade, "Human Cells Revert to Embryo State, Scientists Assert"), although cow mitochondria would not be expected to work with a human nucleus, the mitochondria of chimpanzees and gorillas would be expected to be functional in human cells. In fact, scientists have already made chimeric "geep" (combined sheep and goat), and "camas" (combined camels and lamas), suggesting that the cells and cellular organelles of closely related species would be functionally compatible (see Ruffing et al., Biol. Reprod. (1993) 48(4):889-904; also "Bush telegraph on chimeras," The Daily Telegraph, January 22, 1998, p. 27; "It's a geep: cross-breeding goats and sheep," Time, February 27, 1984, p. 71; "Meet the geep: part goat – part sheep," Science, May 1984, 5: 6). According to Jakovcic et al. (1975, "Sequence homology between mitochondrial DNAs of different eukaryotes," Biochem. 14(10): 2043- 50), evolutionary divergence of mtDNA sequences appears to have occurred at rates similar to that for unique sequence nuclear DNA. --

Q2

The paragraph beginning on line 10 of page 9 (line 21 of page 9 of the substitute specification) is amended as follows:

-- The ability to re-clone cloned mammals and generate a line of cloned mammals that are isogenic for both nuclear and mitochondrial DNA allows for concurrent injection of the cross-species cloned cells containing allogeneic mitochondria into separate mammals, thereby facilitating the retrieval of panels of antibodies and lymphocytes specific for different mitochondrial backgrounds. Methods of recloning cloned mammals based on the observation that nuclear transfer can be used to rejuvenate senescent cells are disclosed in commonly assigned, copending Application Serial No. 09/656,173, filed concurrently herewith and incorporated by reference in its entirety. Of course, it is also possible to generate cloned mammals having isogenic mitochondrial DNA by performing nuclear transfer from a single

Q3

Q3 donor using multiple oocytes or other suitable recipient cells from a single recipient mammal or cell line. Thus the methods of the present invention may also be performed wherein said discs and/or stem cells are injected into separate mammals which are isogenic to the nuclear donor with respect to both nuclear and mitochondrial DNA in order to isolate panels of antibodies and/or lymphocytes. --

The paragraph beginning on line 6 of page 12 (line 21 of page 12 of the substitute specification) is amended as follows:

-- In particular, the immune-compatible tissues and cells generated are useful in methods of providing a patient in need of a transplant with an immune-compatible transplant. Such a method further comprises, in addition to the above steps, transplanting said engineered tissue into a patient. The fact that the present inventors have surprisingly found that cloned cells containing isogenic nuclear DNA and allogeneic mitochondrial DNA do not induce Q4 transplant rejection has particular relevance for transplants which replace native cells suffering from mitochondrial damage, for instance as in amyotrophic lateral sclerosis (ALS), or Leber's hereditary optic neuropathy (LHON). In such cases, cloned tissue having isogenic nuclear DNA and allogeneic mitochondrial DNA that does not induce an immune reaction is the most ideal tissue for transplantation in that such tissue not only provides the closest histocompatibility match, but it also effectuates mitochondrial gene therapy in that tissue containing damaged mitochondria is replaced. --

The paragraph beginning on line 5 of page 15 (line 26 of page 15 of the substitute specification) is amended as follows:

-- In this regard, it is pertinent to note that the present inventors have also discovered that the cloning procedures of the present invention enables the rejuvenation of senescent Q5 cells, thereby foregoing any concerns regarding the genetic age of cloned tissues. The disclosure of U.S. application Serial No. 09/656,173, which is co-owned with the present application, reports the inventors' surprising observations relating to the rejuvenation of primary cells using nuclear transfer, and is herein incorporated in its entirety. The finding that the cloning process rejuvenates older cells is particularly relevant for designing therapeutic tissues expressing more than one heterologous gene, or having more than one

Q5

gene knocked out, because such tissues can be generated by cloning and re-cloning primary cells of the same genetic background. --

The paragraph beginning on line 2 of page 23 (line 5 of page 24 of the substitute specification) is amended as follows:

-- Five micron sections of formalin fixed paraffin embedded tissue were cut and stained with hematoxylin and eosin (H&E). Immunocytochemical analyses were performed using specific antibodies in order to identify the cell type of the retrieved tissues. Histochemical analyses using aldehyde fuschin-alcian blue, and immunocytochemical studies using monoclonal anti-collagen II (Chemicon, St. Louis, MO) were used to identify the engineered cartilage structures. Monoclonal sarcomeric tropomyosin (Sigma, St. Louis, MO) and troponin I (Chemicon, Temecula, CA) antibodies were used to detect skeletal and cardiac muscle fibers, respectively. Immunolabeling was performed using the avidin-biotin detection system. Sections were counterstained with methyl green. --

Q6

IN THE CLAIMS:

Please cancel claims 8-10, 20-28, and 33, and amend claims 1, 38 and 48 as shown below:

1. A method of testing the immune compatibility of cloned cells or tissues in an animal model, comprising:

Q7

a. obtaining a cell from a donor animal;

b. removing the nuclear DNA from a recipient oocyte, transferring the nucleus from said donor cell into the recipient oocyte, and generating an embryo;

c. isolating an embryo having at least one cell, an embryonic disc and/or stem cell from said embryo;